REMARKS

Amendments to the Claims

With this response, claims 1 and 28 are amended, claim 5 is cancelled, and new claims 43 to 60 are added. Claims 1, 6-16, 22, 28 and 32-60 remain pending and under consideration. The amendments to claims 1 and 28 find support, *inter alia*, at pages 8, lines 24 to page 9, line 4 of the specification. New claims 43 to 44 find support in the specification, *inter alia*, at page 41, line 27 to page 42, line 15. New claims 45 to 60 are comparable to the previously presented claims, and additionally find support in the specification, *inter alia*, at page 41, line 25 to page 42, line 22, and at page 46, line 25 to page 47, line 25,

Observation on Previous Response

Initially, Applicant draws the Examiner's attention to an error set forth at page 8, paragraph 2 of the Amendment filed on June 16, 2004 in the above-identified application. The pertinent passage of the Amendment reads as follows:

> According to the report, the presently named inventors are the correct inventive entity of claims 1-27 and 29-31 in the published PCT application. The report also indicates that Dr. Mark Pescovitz was the sole inventor of claim 28 of the published PCT application, a claim that is not pending in this application. Based on these observations, no change is required to the inventive entity of the present application. A copy of the report is provided in the enclosed IDS.

In the above-quoted passage, Applicant erroneously referenced certain claim numbers in the published PCT application. The presently named inventors are the correct inventive entity of claims 1 to 28 and 30 to 31 in the published PCT application. The above-quoted passage incorrectly references claim 28 of the published PCT application. The correct claim number in the published PCT Application is claim 29. Applicant notes that claim 29, or another claim corresponding to this claim, is not pending in the present application, and was not pending at the

time of the previous communication by Applicant. Based on these observations, no change is required to the inventive entity of the present application. A copy of the report referenced in the above-quoted paragraph was provided in the Supplemental IDS filed on June 16.

35 U.S.C.§112 Rejection

The Examiner has maintained the rejection of claims 10, 32, and 41 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for the Examiner's rejection is that a deposit of the hybridoma which produces the 2B8 antibody must be made, and that the deposit must meet the requirements set forth in 37 CFR 1.801-1.809.

Applicant observes that hybridoma HB11388 was deposited with the American Type Culture Collection in a manner that complies with the requirements of 37 CFR 1.801-1.809. For example, a deposit of this hybridoma was made in connection with the issuance of U.S. Patent No. 6,682,734, which, *inter alia*, claims an invention that makes use of an antibody produced by hybridoma HB11388 (see claim 11). Applicant directs the Examiner's attention to column 30, lines 50 to 67, particularly lines 65 to 67, which state:

> Hybridoma 2B8 was deposited with the ATCC on Jun. 22, 1993 under the provisions of the Budapest Treaty. The viability of the culture was determined on Jun. 25, 1993 and the ATCC has assigned this hybridoma the following ATCC deposit number: HB 11388.

Applicant submits that the above-cited passage from the '734 demonstrates that the 2B8 hybridoma has been deposited under the conditions specified in 37 CFR 1.801-1.809. Moreover, as stated on the record of the application that matured into the '734 patent, all restrictions on the

availability of the deposited material to the public were irrevocably removed when the patent was granted. As such, this rejection should be withdrawn.

35 U.S.C.§102(b) Rejection

The Examiner has rejected claims 1, 5-6, 11-16, 22, 28 and 34-39 under 35 U.S.C. §102(b) as anticipated by WO 98/04281 (hereafter "the Davis reference"). The Examiner suggests that the Davis reference anticipates the presently claimed invention because, *inter alia*, various aspects of the presently claimed invention, in the opinion of the Examiner can be found at various locations within the Davis reference. As observed by the Examiner, these include: that an immune cell can be a B-cell (claim 19), a B-cell antigen can be CD20 (claim 23), a therapeutic protein to be administered can be a monoclonal antibody to human CD20 (claim 23), the B-cell mediated disease can be graft versus host disease (claim 21), the "therapeutic proteins" disclosed in the published application can be useful in the treatment of transplanted organ rejection of a variety of organs (page 10, lines 1-3), that monoclonal antibodies can be chimeric, human or humanized (page 7, lines 5-14), that the antibodies can be administered intravenously (page 1, line 14-15, page 20, tables 1-5) or subcutaneously (page 7), that the antibodies can be administered in various dosage regimens that the Examiner believes correspond to the present claims (page 3, line 18; page 10, line 14-15; page 20; and tables 1-5), that the antibodies can be administered in regimens where the second administration increases by at least 50% the systemic exposure of the antibody relative to the first administration (claim 1), and the prophylactic use in transplanted organ rejection (page 10, lines 13-14). Applicant respectfully traverses this rejection.

To establish anticipation under 35 U.S.C.§102, "*every* limitation of a claim must *identically* appear in a single prior art reference." *Gechter v. Davidson*, 116 F.3d 1454, 1457 (Fed. Cir. 1997) (emphasis supplied). Anticipation requires identity. *Tyler Refrigeration v. Kysor Indus. Corp.*, 777 F.2d 687, 227 USPQ 845 (Fed. Cir. 1985). To anticipate, a "reference must clearly and unequivocally disclose the claimed compound or direct *those skilled in the art* to the compound *without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.*" *In re Arkley*, 455 F.2d 586, 587-88(CCPA 1972) (emphasis added); see also, e.g., *Ex parte Pillai*, 2003 WL 23014459, at *4 (Bd. Pat. App. & Inter.2003) ("Anticipation is not established by picking and choosing isolated elements from unrelated portions of a reference and combining them to arrive at the claimed invention."). The identical invention must be shown in as complete detail as is contained in the patent claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 9 USPQ2d 1913 (Fed. Cir. 1985). The claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate. *Glaverbel S.A. v. Northlake Mkt'g & Supp., Inc.*, 45 F.3d 1550, 33 USPQ2d 1496 (Fed. Cir. 1995).

Davis et al. cannot meet these exacting standards required for anticipation under §102(b) for the currently presented claims because it does not disclose a method meeting all of the limitations of the pending claims, as amended.

Claim 1 requires, *inter alia*, use of an antibody that binds to the CD20 antigen on human B lymphocytes in the prevention of rejection of an allogeneic graft in a human. Claim 28, *inter alia*, requires use of an antibody that binds to the CD20 antigen on human B lymphocytes to treat graft versus host or host versus graft disease in a human. There is no disclosure within the Davis publication that anti-CD20 antibodies can or should be used in the two treatment settings

specified in the claims. Rather, at page 10, graft rejection and graft-versus-host diseases are merely listed as two of a wide variety of disorders and illnesses that may be treated by administration of antibodies to "immune cell antigens" (in a generic sense). This teaching is not a teaching that is sufficient under the standards of §102(b), in part because there is no suggestion, let alone a specific disclosure, of use of antibodies that bind to the CD20-antigen, to treat graft rejection and graft-versus-host disease.

Applicant also observes that Davis et al. is generally directed to methods for increasing the systemic exposure of therapeutic proteins which bind to selected antigens on the surface of immune cells. In particular, Davis et al. (page 2, lines 15 to 22) teach that the systemic exposure of therapeutic proteins which bind to selected antigens on the surface of immune cells "is increased by first providing (or administering) a *saturating dose* of the therapeutic protein followed by a second administration of such therapeutic protein, which is given subcutaneously, whereby the *systemic exposure of the second administration is at least 50% greater than an equivalent subcutaneous dose administered without the benefit of the saturating dose*. Davis et al., observe:

> The saturation dose of the instant invention is not equivalent to a loading dose, in which an administered drug, typically an antibiotic, is given iv to rapidly raise the level of antibiotic to its optimum steady state levels. For the instant invention, the kinetics are non-linear and the saturating dose is administered for an entirely different purpose. That is, the initial or saturation dose is intended to bind endogenous target antigens in the lymphatic system in order to allow the second administration of a therapeutic protein, given subcutaneously, to reach the ultimate site(s) of action . . . and to have its maximum therapeutic effect.

See page 9, lines 17 to 25. Davis et al. also teach at page 4, lines 17 to 20 that a "saturating dose" is "the amount of therapeutic protein necessary to completely bind a selected immune cell antigen *in the lymphatic system* such that no appreciable binding of the therapeutic protein to the

immune cell antigen occurs upon subsequent administration(s) of the therapeutic protein." (emphasis added) "No appreciable binding" is defined at page 4, lines 27-30 as meaning "that the difference between the plasma AUC (area under the plasma concentration versus time curve) between a subcutaneous dose which follows the saturating dose and a subcutaneous dose (of the same dosage) that was not preceded by a saturating dose, is at least 2-fold.

These observations indicate, among other things, that Davis et al., does not equate a "saturating dose" with a "therapeutically effective dose" as that term is used by Applicant. Thus, Davis et al. does not teach that administration of a first dose of antibody will or even can be a "therapeutically effective amount." Instead, Davis et al. teach that administration of a "saturating dose" of an antibody should be followed by administration of a second subcutaneous dose of that antibody. Davis et al., teaches that this sequence of steps results in the systemic exposure achieved by the second administration being at least 50% greater than an equivalent subcutaneous dose administered without the benefit of the saturating dose. According to logic of Davis et al, a therapeutically effective amount would not be administered until the second administration of the "immune cell" specific antibody.

As noted above, the present claims require (1) administration of a *therapeutically effective dose* of antibody that binds to the CD20 antigen, and (2) that the therapeutic effect – reduction of circulating levels of B lymphocytes –occur upon the first such administration of the antibody. Because Davis et al., do not teach a method where the first administration of an antibody will be a "therapeutically effective amount" it cannot anticipate the present claims. In addition, newly presented independent claims 45 and 46 require that each dose of antibody be administered through intravenous injection, further distinguishing the present invention from the concept of the Davis et al., method.

The claims of in the Davis et al. publication referenced by the Examiner also do not describe a process that anticipates the present claims. For example, the Examiner points to published claims 19, 21 and 23 to suggest that these claims teach the presently claimed methods. Each of these claims is depends directly or indirectly from claim 1 of that patent. Each of these claims is a further limitation of the method set forth in claim 1, a method that is clearly distinguishable from the present claims. Specifically, claim 1 of the Davis et al., publication requires a first administration of a "saturating dose" of an anti-immune cell antibody. The claim then requires (following this first "saturating" dose) a second subcutaneous administration of the immune-cell antibody. As taught by Davis, a saturating dose is a dose that is sufficient to coat the available cells presenting antigens to which the antibody binds within the lymphatic system. See, page 4, lines 17 to 26. A saturating dose is not a therapeutically effective dose of the antibody, according to Davis et al. In contrast to this regimen in the Davis claims, the present claims define a method of administration of an antibody that binds to the CD20 antigen on human B lymphocytes wherein the antibody, from its first administration, reduces the circulating levels of B lymphocytes to block the immune response or to treat the disease.

The other claims in the Davis et al publication referenced by the Examiner similarly do not teach or disclose a method where antibodies to the CD20 antigen are used to block an immune response to a graft or to treat graft-versus-host disease. As noted above, claim 1 refers to a particular two step method which is not specific either to the antibody used or the immune-cell related disorder. Claim 19 referenced by the Examiner limits claim 1 to methods where the immune-cell related disorder is a B-cell disorder. Claim 23 then further limits claim 19 by specifying that the antibody to treat the "B cell disorder" is an antibody to CD20. Thus, claim 23 does not recite – much less teach – a method where a CD20 antibody is to be used to treat graft

versus host disease or to block an immune response to a graft. Instead, it teaches a two step method of treating an unspecified B-cell related disorder (generically) using a CD20 antibody. In a similar manner, claim 21 limits claims and 19 only by specifying that the B-cell disorder is graft-versus-host disease. It does not, as the Examiner appears to suggest, teach a method where an anti-CD20 antibody is used to treat graft-versus-host disease. Because none of these claims, properly read, teach methods that are the same as the presently claimed methods, these claims cannot be read as anticipating the pending claims.

In view of these points and under the law governing anticipation under §102(b), the Examiner's rejection of claim 1 and claims dependent thereon under §102(b) over the Davis reference is improper. Applicant respectfully requests withdrawal of the rejection of the claims on this basis.

35 U.S.C. §103 Rejection over Davis in view of Business Wire

The Examiner has rejected claims 1, 7-10, 28, 32, 40 and 41 under 35 U.S.C. §103(a) as unpatentable over WO 98/04281 ("Davis et al.") in view of Business Wire (2/24/1998). The Examiner suggests that the claimed invention differs from the Davis reference teachings only in the recitation that the antibody comprises rituximab in claims 7 and 40; that the antibody is conjugated with a cytotoxic agent in claim 8; that the antibody comprisesY2B8 in claims 10, 32, and 41; and wherein the cytotoxic agent is a radioactive compound as set forth in claim 9. The Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time the invention was made to alter the methods disclosed in the Davis publication to use the Y2B8 antibody taught in the Business Wire article and urges that one would have been motivated to do so because Y2B8 exhibits excellent *in vivo* retention of yttrium. The Examiner suggests that it is

apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention and that the invention as a whole was prima facie obvious in the absence of evidence to the contrary. Applicant respectfully traverses this rejection.

Applicant respectfully submits that the Davis et al. and Business Wire references, taken alone or together, would not have rendered the presently claimed methods obvious to a person of skill in the art. As noted above, the Davis et al. publication does not teach either a method for treating graft rejection or of treating graft-versus-host disease using antibodies that bind to the CD20 antigen on human B lymphocytes. Rather, Davis et al., is directed to a *generalized* method for improving the effectiveness of subcutaneous administration of "immune-cell" specific antibodies to treat "immune cell" mediated diseases. In particular, Davis et al. teaches a method requiring a particular sequence of steps. The first such step is administration of what Davis terms a "saturating" dose of the antibody. Following the administration of this saturating dose – which Davis et al., teaches is administered to bind available antigen targets on immune cells present in the lymphatic system – Davis et al., teaches a second step of subcutaneous administration of another dose of the immune-cell specific antibody. Davis et al., teaches that the amount of and purpose for the first administration of the antibody is to coat the immune cells bearing the relevant antigen which are resident in the lymphatic system of the patient. Per the teachings of Davis et al., once the cells in the lymphatic system are coated, the subsequent subcutaneously administered dose of antibody will be able to bypass the lymphatic system and reach the site of action (e.g., an inflamed joint in the case of rheumatoid arthritis), and presumably, exhibit the desired therapeutic effect.

Davis et al., properly read, also provides only a generalized teaching of use of its improved methods in treating a wide variety of "immune cell mediated diseases" using a wide

variety of types of antibodies that target or bind an antigen expressed on the surface of immune cells. According to Davis et al., the CD20 antigen is one of twelve specifically enumerated "T (or B) cell" antigens "which are involved with T (or B cell) mediated disorders." See, e.g., page 5, lines 1 to 7, and page 14, line 25 to page 15, line 18. Davis et al., provides that "immune cell mediated disease states" include "lymphomas (T and B cell), various leukemias, infectious diseases (e.g., AIDS), transplantation, autoimmune and inflammatory diseases." See, page 9, lines 28 to 31. Thus, while Davis et al., posits that its method will yield benefits in effectiveness of a variety of antibody treatments, it does not specifically describe a method of administering an anti-CD20 antibody to block an immune response to an allogeneic graft in a human as set forth in claim 1, or to treat graft-versus-host or host-versus-graft disease in a human, wherein the graft is from a human having the same or a different genetic origin as the human being treated as set forth in claim 28. Applicant submits that a person of skill in the art would not read the Davis et al., disclosure to suggest that an antibody to any of a wide variety of "immune cell" antigens identified by Davis et al., would be useful in treating every one of the "immune cell mediated disease states" listed at page 9 and 10, and thus, the Davis et al., publication does not actually teach what the Examiner represents that it does.

As explained above, the present claims, in contrast to Davis et al., require administration of specific antibodies (i.e., those that bind to the CD20 antigen on B lymphocytes) which, from the first administration of the antibodies, reduce circulating levels of B lymphocytes to block an immune response to an allogeneic graft (claim 1) or treat graft-versus-host or host-versus-graft disease (claim 28). Under the logic of the Davis et al., method, the administration of a "saturating" dose of antibody would not be a "therapeutically effective" dose, in part, because the purpose Davis et al., teach for administering that dose is to coat the available cells in the

lymphatic system bearing the relevant antigen, and because Davis et al., teach that subsequently administered antibodies will reach the desired site of action and exhibit the intended therapeutic effect. Moreover, particularly in reference to newly presented claims 45 and 46, Davis et al., require administration of at least one dose of the antibody through subcutaneous injection.

The deficiencies of Davis et al. relative to the present claims are not remedied by the teaching of the Business Wire article. Instead, the Business Wire article merely reports on initiation of a Phase III trial incorporating both of IDEC Pharmaceutical's treatments for relapsed or refractory B-cell non-Hodgkin's lymphoma, IDEC-Y2B8, and the recently approved immunotherapy, Rituxan. Rituxan is disclosed as being used in the regimen to clear malignant and normal B cells from the blood, allowing IDEC-Y2B8 to penetrate the lymphatic system and target radiation to lymphatic tumors.

There is no discussion in the Business Wire article cited by the Examiner of use of antibodies to the CD20 antigen to treat graft rejections or graft-versus-host disease. One of ordinary skill in the art thus would not look to Business Wire for guidance in altering the methods and disclosure of the Davis et al., publication, either to select an antibody to CD20 to block immune responses to allogeneic grafts or to treat graft versus host disease, or to devise a new treatment regimen where upon each administration of the antibody, circulating levels of B cells would be reduced in the patient to exhibit the desired therapeutic effect. Applicant also maintains that even armed with knowledge that rituximab achieves selective depletion of B-lymphocytes in patients with B-cell lymphomas, such as non-Hodgkins lymphoma, a person of skill would not have been motivated from the Business Wire article or Davis et al. to arrive at the presently claimed method.

For the reasons set forth above, Davis et al. does not teach or suggest administration of a therapeutically effective amount of an antibody which binds to CD20 to block an immune response to an allogeneic graft as set forth in claim 1, or to treat graft-versus-host or host-versus-graft disease as set forth in claim 28. The teachings of the Business Wire article do not cure the fundamental defects of Davis et al. Applicant accordingly requests withdrawal of this rejection.

35 U.S.C. Rejection over Davis in view of US Patent No. 6,498,181

The Examiner has rejected claims 1, 8-10, 28, 33, and 42 under 35 U.S.C. §103(a) as unpatentable over WO 98/04281 ("Davis et al.") in view of U.S. Patent No. 6,498,181 (hereafter "Gehlsen"). The Examiner urges that the claimed invention differs from the reference teachings only by the recitation that the antibody is conjugated with a cytotoxic agent in claim 8, ^{131}I-B1 in claims 10, 33, and 42 wherein the cytotoxic agent is a radioactive compound in claim 9. The Examiner urges that the '181 patent teaches ^{131}I labeled anti-B1; (Bexxar) mAb, raised to the CD-20 antigens that are expressed on the surface of mature B-cells, is one example of a radiolabeled mAb that has been successful in treating follicular non-Hodgkins lymphoma in recent clinical trials. The Examiner urges that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody to human CD20 taught by the Davis publication with the ^{131}I-B1 antibody as taught by the Gehlsen patent. The Examiner has taken the position that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because ^{131}I-B1 has been successful in recent clinical trials as taught by the Gehlsen patent.

As noted in the response to the rejection in Paragraph 9 of the last Office Action, Davis et al., does not teach what the Examiner has suggested. In particular, Davis et al., do not disclose a

method of blocking an immune response to a graft or treatment of graft versus host disease using antibodies that bind to the CD20 antigen, wherein those antibodies, upon each administration, deplete circulating B cell populations to exhibit the desired therapeutic effect. Rather, Davis et al., is directed to generalized methods of enhancing availability of administered antibodies, for the reasons set forth above.

The Gehlsen patent does not cure the deficiencies of the Davis reference. Instead, Gehlsen is directed to methods of treating cancer. The cancer therapy includes surgery, radiation, immunotherapy, and the administration of an agent which enhances the humoral response of the patient or any combination thereof. At col. 9, lines 3-12, Gehlsen teaches that histamine can be administered in conjunction with an antibody therapy. Gehlsen teaches:

> According to the one aspect of this embodiment, a radioactive monoclonal antibody is administered in conjunction with histamine. Preferably, histamine is administered for 1-2 weeks before the antibody therapy to raise the stable concentration of histamine in the patient's blood to at least about 0.2μM. After a stable level of blood histamine of at least about 0.2μM has been achieved, a radiolabeled mAb directed to a cancer cell antigen is administered in conjunction with histamine treatment to the patient.

At col. 9, lines 22-28, Gehlsen teaches:

> Preferable radiolabeled mAbs are able to deliver more than 6000 rads to the tumor and have sufficient affinity so that the patient's bone marrow is not exposed to more than 300 rads. ^{131}I labeled anti-B1(Bexxar) mAb, raised to the CD-20 antigens that are expressed on the surface of mature B-cells, is one example of a radiolabeled mAb that has seen successful in treating follicular non-Hodgkins lymphoma in recent clinical trials.

One of ordinary skill in the art would not look to Gehlsen for guidance in blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease, in part because Gehlsen is directed to the use of the Bexxar anti-B1 monoclonal antibody in the treatment of *cancerous* conditions, specifically non-Hodgkins lymphoma. The pending claims of

the present application specifically exclude therapy of malignant or cancerous conditions. (See Applicants' specification at page 5, lines 5-6).

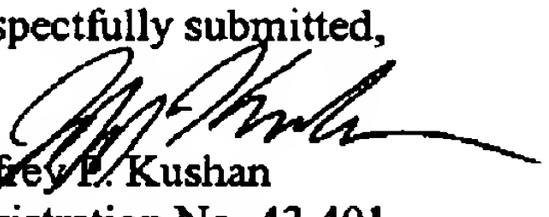
Accordingly, the cited publications do not establish a *prima facie* case of obviousness of the rejected claims. Applicant accordingly requests withdrawal of this rejection.

CONCLUSION

In light of the above amendments and remarks, Applicant respectfully submits that all pending claims as currently presented are in condition for allowance. If, for any reason, the Examiner disagrees, he is requested to contact the undersigned attorney at 202-736-8914 in an effort to resolve any matter still outstanding *before* issuing another action.

Favorable reconsideration is respectfully requested.

Respectfully submitted,



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